## DESCRIPTION OF THE PROPOSED EXPERIMENT IN NON TECHNICAL LANGUAGE

Cystic fibrosis (CF) is a serious genetic disease characterized by obstruction of the airways with thick mucous and frequent infections which destroy lung tissue. The disease is fatal with an average life expectancy of approximately 30 years [1]. The gene which is abnormal in CF is normally responsible for producing a protein called the cystic fibrosis transmembrane conductance regulator, or CFTR. This protein controls the salt balance in the airways of the lungs; when the protein is not normal, excessive thick mucous is produced resulting in the complications described above. Treatment, which includes antibiotics, good nutrition and mucous clearance, has improved; however, no treatment corrects the basic underlying defect, and the lung problems invariably worsen with time.

Because cystic fibrosis is a genetic disease, adding a normal CFTR gene to cells that line the affected airways could restore normal function to these cells and thereby correct the problems associated with the disease. This approach is called gene therapy. In laboratory studies we have successfully inserted a normal CFTR gene into airway cells of animals and cells grown in culture. A lipid (a fat-like molecule) was used to carry the CFTR gene into these cells. Studies in laboratory animals have shown that the lipid:pDNA mixture does not cause serious damage to the lung at low to medium doses, although at high doses it can cause a more severe inflammatory response.

The proposed protocol is designed to evaluate 67A:pCF1-CFTR for its ability to transfer the cystic fibrosis transmembrane conductance regulator (CFTR) gene to the lungs of CF patients lacking adequate functional CFTR.

In order to minimize the risk to CF patients, the dose to be used for aerosol delivery to the lungs of CF patients was determined by testing the lipid formulation (67A) alone in the lungs of normal volunteers in Genzyme clinical trial CF95L-1101: *Safety of aerosol administration of escalating doses of a cationic lipid formulation to the lungs of normal volunteers.* The highest tested dose (114.4 mg 67A) was determined to be safe by the absence of systemic toxicity and absence of a clinically significant change in lung function. The cationic lipid formulation 67A will be complexed with pCF1-CFTR DNA at a 6:8 molar ratio (total lipid @ 14.3 mg/mL:pCF1-CFTR @ 2.64 mg/mL) for aerosol administration of 16 mL to each CF patient in this trial.

An aerosol of **67A:pCF1-CFTR** will be generated using a Pari LC jet Plus Nebulizer. The aerosol will be generated following breath actuation of the nebulizer which will release 2 seconds of aerosol. Exhaled air/aerosol will pass through a breathing circuit filter prior to release. A nasal adapter will be fitted to the nebulizer for delivery of the material to the nose in the nasal section of the trial. The complex will be initially aerosolized to the lung followed six (6) days later by aerosolization to the nasal mucosa.

Safety of the applications will be assessed during the study by both clinical exam and routine laboratory tests. Transfer of the CFTR gene into the cells lining the nose of CF patients will be tested in two ways. In healthy individuals a small electrical charge or voltage can be measured in the cells lining the nose; this voltage is abnormal in CF patients. The voltage in the nose of CF patients will be measured before and after gene delivery. Return of this voltage towards normal levels will signal that the CFTR gene has been delivered successfully. Second, a brush and biopsies will be used to collect treated cells lining the nose of CF patients after gene delivery. These cells will be tested for the presence of the normal CFTR gene to confirm successful gene transfer. Transfer of the gene into cells lining the lower airway will be evaluated by molecular analysis of lower airway cells obtained by bronchoscopic brushing and biopsies.